IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: BROD	§	**ART UNIT: 1761**
	§	
FILED: October 8, 1997	§	
	§	
SERIAL NO.: 08/946,710	§	**EXAMINER: SAYALA, C**
	§	
FOR: METHODS OF TREATING	§	
AUTO-IMMUNE DISEASES	§	**DOCKET: D5716CIP4**
USING TYPE ONE INTERFERONS	§	

Box NON-FEE AMENDMENT
Assistant Commissioner of Patents
Washington, D.C. 20231

Dear Sir:

DECLARATION UNDER 37 C.F.R. 1.132

JOHN WILLIAM LINDSEY does hereby state as follows:

I am an Assistant Professor of Neurology at the University of Texas Health Science Center in Houston, Texas. I am skilled in the areas of autoimmune diseases generally and multiple sclerosis, diabetes and rheumatoid arthritis in particular. My *curriculum vitae* is attached hereto. I have read U. S. patent application Serial No. 08/946,710, filed on October 8, 1997, and I am aware of the contents of, and responses to, the Office Actions, including all prior art cited against the '710 application.

The Applicant's invention claimed in the above-referenced application related specifically to the oral administration, i.e., ingestion,

of interferons to treat autoimmune diseases, such as multiple sclerosis, diabetes or rheumatoid arthritis. A main issue regarding patentability is: would it have been obvious to a person having ordinary skill in this art at the time the parent application was filed, i.e., April 1994, to orally administer interferon to treat autoimmune diseases in view of the **Cummins** (US Patent 5,019,382). For the reasons delineated *infra*, the answer is clearly no.

The **Cummins** patent presents anecdotal evidence regarding administration of alpha interferon to treat an extremely limited sample of humans with autoimmune disease. **Cummins** does not provide a person with ordinary skill in this art with a reasonable expectation of being able to successfully treat an autoimmune disease such as multiple sclerosis, diabetes or rheumatoid arthritis by orally administering alpha interferon. It is my considered opinion that a person of ordinary skill in this art (e.g. a physician treating multiple sclerosis, diabetes or rheumatoid arthritis patients) would not have had a reasonable expectation of being able to successfully treat an autoimmune disease such as multiple sclerosis, diabetes or rheumatoid arthritis, by orally administering alpha interferon after having read **Cummins.**

In **Cummins**, two patients with rheumatoid arthritis and one patient with multiple sclerosis were given alpha interferon. The

interferon was administered orally, intending to promote contact with the oral or pharyngeal mucosa. **Cummins** stressed that contact with the oral or pharyngeal mucosa should be maximized. The interferon was retained in the mouth for about one minute, and then either swallowed or discharged from the mouth. Clearly, contact of the interferon solution with gastric or intestinal mucosa was regarded as inconsequential, while contact with the oral or pharyngeal mucosa was essential.

In contrast, the instant invention teaches the ingestion of interferon. In Applicant's animal experiments, the interferon was fed through a needle inserted directly into the stomach or duodenum of the animal, i.e., there was no contact with the oral or pharyngeal mucosa. In Applicant's clinical studies with human subjects, the interferon was "ingested", which briefly exposed the oral mucosa to the interferon, but no attempts at maximizing contact with the oral mucosa were made nor would there have been any significant absorption of the alpha interferon through the oral or pharyngeal mucosa.

The recommended dose of interferon is an additional reason why **Cummins** does not render the instant invention obvious. The dose stated in **Cummins** is 0.1 to 5 IU/lb body weight/ day, while the dose taught by Dr. Brod is 50 to 25,000 IU/kg. These dose ranges do not

overlap, and the doses found to be effective in the instant invention are around two orders of magnitude, or 100 times, higher than the maximum dose recommended by **Cummins**. The Examiner argues that the **Shibutani et al**. reference, combined with **Cummins**, would suggest use of such higher doses. However, **Shibutani et al**. merely describes the lack of toxicity of human beta interferon given at varying doses intravenously or orally to mice and rats. This reference in no way teaches or suggests a useful dosage range of interferon for treatment of autoimmune diseases.

Additional references cited in support of the rejection of the instant application were **Gross** et al., **Giron** et al., the abstract of **WO 94/20122** and the patent of **Sobel** (U.S. Patent 5,624,895). **Gross** et al. is an abstract which reports the use of alpha interferon injected subcutaneously to treat the condylomata acuminata in a patient who coincidentally had diabetes. The interferon was not given in an attempt to treat or prevent the diabetes and no benefit on diabetes was observed. This abstract is thus irrelevant to the instant invention.

Giron et al. is an abstract which describes the antiviral effect of interferons on encephalomyocarditis infection in mice. This viral infection can also cause diabetes. The route of interferon administration is not specified in the abstract, nor is the type of

interferon used. This work is of dubious relevance to spontaneously occurring diabetes in humans and the NOD mouse model of human autoimmune diabetes.

WO 94/20122 is an abstract of a patent application describing methods to treat "an asymptomatic preclinical autoimmune state in a mammal" or to inhibit "rejection of transplanted islet cells or a pancreas in a mammal", neither of which pertain to the instant invention.

Sobel (U.S. Patent 5,624,895) describes the use of gamma interferon for prevention of diabetes. This patent does not render the instant invention obvious, because of the differences between gamma interferon and alpha and beta interferons. Gamma interferon is a type II interferon, whereas alpha and beta interferons are type I interferons. These two types of interferon are made by different types of cells, and in many cases have opposing effects. The most striking example of this is the effects of the two types of interferons on multiple sclerosis. In a controlled study, administration of gamma interferon caused the disease condition to worsen, necessitating early termination. In contrast, alpha and beta interferons have had a beneficial effect on disease in several well-designed clinical trials. Although the agents share the name interferon, their actions are quite distinct, and knowledge of the effect

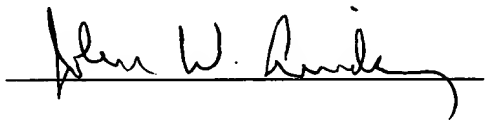
of gamma interferon does not make the effect of alpha or beta interferon obvious.

Clearly, one with ordinary skill in the art of autoimmune pathophysiology and treatment would not expect clinical efficacy in humans from the oral administration of alpha interferon after having read the **Cummins** and the **Shibutani** et al., **Gross** et al., **Giron** et al., **WO 94/20122** and **Sobel** references. In fact, the opposite expectation that ingesting interferon would have no effect is more reasonable. Interferon is a protein, and proteins are broken down in the gastrointestinal tract. Thus, a person having ordinary skill in this art would expect interferon to be inactive when swallowed. Hence, the claimed methods are not only not obvious to one of ordinary skill, they are also counterintuitive.

In conclusion, the extremely limited clinical anecdotes presented in **Cummins** would not provide a person with ordinary skill in this art with a reasonable expectation of being able to successfully treat an autoimmune disease such as multiple sclerosis, diabetes or rheumatoid arthritis by orally administering alpha interferon. In my opinion, such a person would not have contemplated the approach of the instant invention to treat autoimmune diseases after having read

the **Cummins** and **Shibutani** et al., **Gross** et al., **Giron** et al., **WO 94/20122** and **Sobel** references.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title I8 of the United States code, and that such willful false statements may jeopardize the validity of the application or patent issued thereon.



DATE 8/12/98 **John William Lindsey, M.D.**

Curriculum Vitae and Bibliography

NAME: John William Lindsey, MD

PRESENT TITLE: Assistant Professor of Neurology

ADDRESS: Department of Neurology
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Houston, TX 77030

BIRTHDATE: May 23, 1960

CITIZENSHIP: United States of America

UNDERGRADUATE EDUCATION:

1978-1981 B.A. in Chemistry, *summa cum laude*
Rice University, Houston, TX

GRADUATE EDUCATION:

1985-1986 M.Sc. in Physiology, Oxford University, Oxford, England
Thesis: The effect of prism adaptation on the activity of brainstem near-response neurons.

1982-1987 M.D., Harvard Medical School, Boston, MA

POSTGRADUATE TRAINING:

1987-1988 Intern in Medicine, Brigham and Women's Hospital, Boston, MA

1988-1990 Resident in Neurology, Stanford University Medical Center, Stanford, CA

1990-1991 Chief Resident in Neurology, Stanford University Medical Center, Stanford, CA

1991-1993 Research Fellow in Neuroimmunology with Dr. Lawrence Steinman, Stanford University Medical Center, Stanford, CA

ACADEMIC APPOINTMENTS:

1993-present Assistant Professor of Neurology, University of Texas--Houston Medical School

HOSPITAL APPOINTMENTS:

1992-1993 Provisional Medical Staff, Stanford University Hospital, Stanford, CA

1993-present Staff Physician in Neurology, Hermann Hospital, Houston, TX

1996-present Assistant Attending Physician in Neurology, LBJ General Hospital, Harris County Hospital District, Houston, TX

LICENSURE:

1988-present	California, G64115 (inactive status since 1998)
1993-present	Texas, J5387

CERTIFICATION:

1988	National Board of Medical Examiners, Certificate #327426
1993	Diplomate in Neurology, American Board of Psychiatry and Neurology, Certificate #037573

PROFESSIONAL ORGANIZATIONS (AND COMMITTEES OF THESE):

1990-present	American Academy of Neurology
1991-present	American Association for the Advancement of Science

HONORS AND AWARDS:

1981	B.A. *summa cum laude*
1981	Phi Beta Kappa
1990-1991	Chief Resident in Neurology, Stanford University Medical Center, Stanford, CA
1991-1993	Dana Fellowship in Neurosciences

EDITORIAL POSITIONS:
SERVICE ON NATIONAL GRANT REVIEW PANELS, STUDY SECTIONS, AND COMMITTEES:
SERVICE ON THE UNIVERSITY OF TEXAS-HOUSTON HEALTH SCIENCE CENTER COMMITTEES:

SERVICE ON THE UNIVERSITY OF TEXAS-HOUSTON MEDICAL SCHOOL COMMITTEES:

1995-present	Member of Faculty Senate
1998-present	Faculty Interviewer for Admissions Committee

SERVICE ON GRADUATE SCHOOL COMMITTEES:

1997-present	Advisory Committee member for Sara Nemanic, PhD candidate, Department of Neurobiology and Anatomy
1998-present	Advisory Committee member for Aurora Seminara, PhD candidate, Department of Neurology

SERVICE ON UTHMS AFFILIATED HOSPITAL COMMITTEES:

SERVICE TO THE COMMUNITY:

1993-present	Member, Medical Advisory Committee, Southeast Texas Chapter of the National Multiple Sclerosis Society
Sept. 24, 1994	"MS—Diagnosis, Prognosis, and Treatment", Newly Diagnosed Workshop, Southeast Texas Chapter of the National MS Society, Houston, TX
Oct. 29, 1994	"Recent Progress in Multiple Sclerosis", Annual Meeting of the West Texas Chapter of the National MS Society, Midland, TX
Dec. 9, 1995	"New Therapies for Multiple Sclerosis", Annual Meeting of the West Texas Chapter of the National MS Society, Midland, TX
Feb. 17, 1996	"Progress in Treatment of Multiple Sclerosis", Regional Meeting of the Southeast Texas Chapter of the National MS Society, Austin, TX
Jan. 18, 1997	"Current Therapy in Multiple Sclerosis", Regional Meeting of the Southeast Texas Chapter of the National MS Society, Beaumont, TX
May 21, 1998	"New Treatments for Multiple Sclerosis", Spring-Klein MS Support Group, Spring, TX

SPONSORSHIP OF CANDIDATES FOR POSTGRADUATE DEGREE:

SPONSORSHIP OF POSTDOCTORAL FELLOWS:

CURRENT TEACHING RESPONSIBILITIES:

1994-1996	The Neurologic Examination, Physical Diagnosis Course, Second Year Students
1994-1996	CNS Infections, Neurology Clinical Clerkship, Fourth Year Students
1994-present	Multiple Sclerosis, Neurology Clinical Clerkship, Fourth Year Students
1994-1996	Neurology Case Discussions, First Year Students

CURRENT GRANT SUPPORT:

PRINCIPAL INVESTIGATOR:

Neurocrine Biosciences: Double-Blind, Randomized, Placebo-Controlled Evaluation of the Safety, Tolerability, and Pharmacokinetics of NBI-5788 in Patients with Multiple Sclerosis, Protocol 01, 9/1/96-9/1/98; direct costs $138,000.

Teva Pharmaceuticals USA and Teva-Marion Partners: Open Label Study to Evaluate the Safety of Copaxone and to Monitor the Neurologic Course of Disease in Multiple Sclerosis Patients Treated with Copaxone, 4/1/98-3/31/00; direct costs $104,490.

CO-INVESTIGATOR

Clayton Foundation for Research: Viral Mimicry and Multiple Sclerosis, 1/1/93-12/31/98; direct costs awarded to date: $609,795; current year $142,737, Dr. Jerry Wolinsky principal investigator.

TEVA Pharmaceuticals: Preclinical studies of copolymer 1, 10/1/96-9/30/98; projected direct costs $207,659; Dr. Jerry Wolinsky principal investigator.

PAST GRANT SUPPORT:

Athena Neurosciences: A multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of Tizanidine and the relationship of plasma concentrations to the changes in muscle tone and common adverse events: 8/1/94-7/31/95; direct costs $63,938, Dr. Jerry Wolinsky principal investigator.

Athena Neurosciences: A multicenter, open-label, long-term study to evaluate the safety of Tizanidine tablets in patients suffering from spasticity due to multiple sclerosis: 7/31/95-4/30/97, direct costs $82,043, Dr. Jerry Wolinsky principal investigator.

University of Texas-Houston Research Council: Immune Regulation in the Central Nervous System, 3/31/96-3/31/97, $26,121.

Pharmacia and Upjohn: A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Roquinimex (Linomide) in Relapsing-Remitting and Secondary Progressive Multiple Sclerosis. 3/1/96-12/9/97, direct costs $180,290.

TEVA Pharmaceuticals: Open label study to evaluate the safety of Copaxone and to monitor the neurologic course of disease in Multiple Sclerosis patients treated with Copaxone, 8/12/94-8/11/98; estimated direct costs $148,706; Dr. Jerry Wolinsky principal investigator, subcontract through University of Maryland.

PUBLICATIONS:

A. Abstracts

1. JW Morley, **JW Lindsey**, and SJ Judge. Changes in the activity of brainstem near response neurons induced by prism adaptation. *Soc Neurosci Abstr* 12:460, 1986.
2. S Hodgkinson, **J Lindsey**, M Allegretta, R Bell, D Mitchell, T Tram, L Dorfman, D Enzmann, and L Steinman. Phase 1 study of chimeric anti-CD4 monoclonal antibody in multiple sclerosis. *Neurology* 42(Suppl 3):S209, 1992.
3. **JW Lindsey**, S Hodgkinson, R Mehta, D Enzmann, M Sanders, and L Steinman. Phase 1 study of repeated treatment with chimeric anti-CD4 monoclonal antibody in multiple sclerosis. *Neurology* 43(Suppl 2):492S, 1993.
4. **JW Lindsey**. Reinduction of experimental autoimmune encephalomyelitis. *Ann Neurol* 36:290, 1994.
5. JS Wolinsky, P Narayana, T Doyle, and **JW Lindsey**. Serial 2D proton magnetic resonance spectrosopic imaging (MRSI) of multiple sclerosis. *Neurology* 45(Suppl 4):A282, 1995.
6. PA Narayana, JS Wolinsky, TJ Doyle, and **JW Lindsey**. Serial proton magnetic resonance imaging in multiple sclerosis. *Radiology*, 1995.
7. **JW Lindsey**. Epitope spreading in reinduced experimental autoimmune encephalomyelitis. *Neurology* 46(Suppl):A295, 1996.
8. V Venkataraman, C Villar-Cordova, V Puduvalli, **JW Lindsey**. Unusual MRI abnormalities in a non-immunocompromised patient with varicella-zoster meningoencephalitis. American Soc. Neuroimaging, 1996.

9. **JW Lindsey**, MR Malone, and FJ Vriesendorp. Fas Ligand expression in the central nervous system. *Neurology* 48(Suppl. 2):A426, 1997.
10. **JW Lindsey**, FD Lublin, SR Stark, JP Antel, JJ Oger, RM Erwin, AC Evans. Double-blind, randomized, placebo-controlled evaluation of the safety, tolerability, and pharmacokinetics of CGP 77116 in patients with multiple sclerosis. *Neurology*, 50(Suppl. 4):A149, 1998.

B. Refereed Original Articles in Journals

1. SE Dessens, CL Merrill, RJ Saxton, RL Ilaria, **JW Lindsey**, and LJ Wilson. Cytochrome oxidase models. 3. Spin coupling across imidazolate bridges in binuclear metalloporphyrin complexes of iron and copper. *J Am Chem Soc* 104:4357-4361, 1982.
2. M Hallett, **JW Lindsey**, BD Adelstein, and PO Riley. Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. *Neurology* 35:1374-1377, 1985.
3. JW Morley, **JW Lindsey**, and SJ Judge. Prism adaptation in a strabismic monkey. *Clin Vision Sci* 3:1-8, 1988.
4. **JW Lindsey**, GW Albers, and L Steinman. Recurrent transverse myelitis, myasthenia gravis, and autoantibodies. *Ann Neurol* 32:407-409, 1992.
5. JW Morley, SJ Judge, and **JW Lindsey**. Role of monkey midbrain near-response neurons in phoria adaptation. *J Neurophysiol* 67:1475-1492, 1992.
6. PC Lee, CD Gocke, ED Harris, ME Anderson, CJ Bergin, JM Price, and **JW Lindsey**. 47-year-old woman with six-week history of lower extremity weakness and eosinophilia. *West J Med* 156:517-522, 1992.
7. RB Bell, **JW Lindsey**, RA Sobel, S Hodgkinson, and L Steinman. Diverse T cell receptor Vβ gene usage in the central nervous system in experimental allergic encephalomyelitis. *J Immunol* 150:4085-4092, 1993.
8. NA Rao, YM Naidu, R Bell, **JW Lindsey**, G Pararajasegaram, Y Sun, and L Steinman. Usage of T cell receptor beta-chain variable gene is highly restricted at the site of inflammation in murine autoimmune uveitis. *J Immunol* 150:5716-5721, 1993.
9. **JW Lindsey** and L Steinman. Competitive PCR quantification of CD4, CD8, ICAM-1, VCAM-1 and MHC Class II mRNA in the central nervous system during development and resolution of experimental allergic encephalomyelitis. *J Neuroimmunol* 48:227-234, 1993.
10. **JW Lindsey**, S Hodgkinson, R Mehta, RC Siegel, DJ Mitchell, M Lim, C Piercy, T Tram, L Dorfman, D Enzmann, and L Steinman. Phase 1 clinical trial of chimeric monoclonal anti-CD4 antibody in multiple sclerosis. *Neurology* 44:413-419, 1994.
11. **JW Lindsey**, S Hodgkinson, R Mehta, D Mitchell, D Enzmann, and L Steinman. Repeated treatment with chimeric anti-CD4 antibody in multiple sclerosis. *Ann Neurol* 36:183-189, 1994.
12. **JW Lindsey**, M Pappolla, and L Steinman. Reinduction of experimental autoimmune encephalomyelitis in mice. *Cell Immunol* 162:235-240, 1995.
13. **JW Lindsey**. Characteristics of initial and reinduced experimental autoimmune encephalomyelitis. *Immunogenetics* 44:292-297, 1996.
14. PW Nance, WA Sheremata, SG Lynch, T Vollmer, S Hudson, GS Francis, P O'Connor, JA Cohen, RT Schapiro, R Whitham, MK Mass, **JW Lindsey**, and K Shellenberger. Relationship of the antispasticity effect of tizanidine to plasma concentration in patients with multiple sclerosis. *Arch Neurol* 54:731-736, 1997.

15. **JW Lindsey**, RH Kerman, JS Wolinsky. T cell-T cell activation in multiple sclerosis. *Multiple Sclerosis Clin Lab Res* 3:238-242, 1997.
16. KP Johnson, BR Brooks, JA Cohen, CC Ford, J Goldstein, RP Lisak, LW Myers, HS Panitch, JW Rose, RB Schiffer, T Vollmer, LP Weiner, JS Wolinsky, and the Copolymer 1 Multiple Sclerosis Study Group. Extended use of Glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. *Neurology* 50:701-708, 1998.
17. **JW Lindsey**. Use of reinduced EAE to evaluate the importance of epitope spread. *Int Immunol* 10:743-748, 1998.

C. Invited Articles (Reviews, Editorials, etc.) in Journals

1. SA Brod, **JW Lindsey**, and JS Wolinsky. Multiple sclerosis: Pathogenesis and Immunotherapy. *Am Family Physician* 54:1301-1311, 1996.

D. Chapters

1. L Steinman, **JW Lindsey**, S Alters, and S Hodgkinson. From treatment of experimental allergic encephalomyelitis to clinical trials in multiple sclerosis. In *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*. JF Bach, ed. Marcel Dekker, New York, pp 253-260, 1993.
2. **JW Lindsey** and L Steinman. Monoclonal antibodies in the treatment of multiple sclerosis. In *Handbook of Multiple Sclerosis*, 2nd Ed., SD Cook, ed. Marcel Dekker, New York, pp 567-584, 1996.
3. **JW Lindsey**, SA Brod, and JS Wolinsky. Multiple sclerosis. In *Current Therapy in Neurologic Disease*, 5th Ed., RT Johnson and JW Griffin, eds. Mosby Year-Book, St. Louis, pp 178-182, 1996.
4. **JW Lindsey**. Immunotherapy with monoclonal anti-CD4 antibodies. In *Weir's Handbook of Experimental Immunology*, 5th ed., LA Herzenberg, DM Weir, LA Herzenberg, and C Blackwell, eds. Blackwell Scientific, Oxford, pp 195.1-195.9, 1996.
5. JS Wolinsky, PA Narayana, TJ Doyle, and **JW Lindsey**. Pathological mechanisms in central nervous system demyelination. In *Frontiers in Multiple Sclerosis: Clinical Research and Therapy*, O Abramsky and H Ovadia, eds., Martin Dunitz Limited, London, pp 87-95, 1997.
6. **JW Lindsey**, SA Brod, and JS Wolinsky. Multiple sclerosis. In *Current Therapy in Adult Medicine*, 4th ed., JP Kassirer and HL Greene II, eds. Mosby Year-Book, St. Louis, pp 1403-1407, 1997.
7. **JW Lindsey** and JS Wolinsky. Demyelinating diseases. In *Scientific American Medicine*, DC Dale and DD Federman, eds., Scientific American, New York, Section 11, Chapter IX, pp. 1-11, 1997.

E. Books

F. Other Professional Communications

1. **JW Lindsey**. "Amyotrophic Lateral Sclerosis", Department of Medicine Clinicopathologic Conference, University of Texas-Houston, April 18, 1994.
2. **JW Lindsey**. "Essentials of Neuroimmunology", Multiple Sclerosis Update, Houston, TX, Sept. 22, 1995.

3. **JW Lindsey**. "Immune Privilege in the Central Nervous System: Implications for Multiple Sclerosis", Department of Neurology Grand Rounds, University of Texas-Houston, Oct. 18, 1996.
4. **JW Lindsey**. "Immunoregulatory Effects of Myelin Basic Protein", Department of Neurology Research Conference, University of Texas-Houston, Dec. 19, 1996.
5. **JW Lindsey**. "Multiple Sclerosis: Diagnosis and Diagnostic Pitfalls", Neurology Update, Houston, TX, Feb 21, 1997.
6. **JW Lindsey**. "Management of Spasticity in Multiple Sclerosis", Houston, TX, June 13, 1997.